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Female-specific association among I, J and K mitochondrial genetic haplogroups and cancer: A longitudinal cohort study

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Abstract

Recent studies highlighted the role of mitochondrial dysregulation in cancer, suggesting that the different mitochondrial haplogroups might play a role in tumorigenesis and risk of cancer development. Our aim is to investigate whether any mitochondrial haplogroups carried a significant higher risk of cancer development in a large prospective cohort of North American people. The haplogroup assignment was performed by a combination of sequencing and PCR-RFLP techniques. Our specific outcome of interest was the incidence of any cancer during follow-up period. Overall, 3222 participants were included in the analysis. Women having I, J, K haplogroup reported a significant higher incidence of cancer compared to people with other haplogroups ($p < 0.0001$), whilst in men non association was found. In the multivariate analysis, women having I, J, K mitochondrial haplogroup reported a 50% increased risk of cancer (HR = 1.50; 95%CI: 1.04–2.16; $p = 0.03$). This gender-linked association may be partly explained by the role of mitochondrial function in female-specific (e.g. BRCA-driven) oncogenesis, but further studies are needed to better understand this potential correlation. Our findings may have important implications for cancer epidemiology and prevention.

Introduction

Mitochondrial genome and haplogroups

The human mitochondrial genome consists of 16,569 base pairs encoding 37 genes and finally 13 proteins [1]. These proteins are involved in several mechanisms important for cellular function and survival [1]. Similarly to nuclear DNA, also mitochondrial DNA is based on a dynamic balance and can undergo to frequent mutations [1], [2]. Defects in repair or recombination can lead to the formation of single nucleotide polymorphisms (SNPs). Clusters of these specific SNPs in the mitochondrial genome define the so called “mitochondrial haplogroups”. They are defined by unique sets of SNPs, and reflect specific ancestral populations as a result of the continuous accumulation of mitochondrial mutations through maternal lineages [3], [4].

Mitochondrial function and its potential role in tumorigenesis

Basing also on this evolutionistic point of view, it is widely accepted that the biology of mitochondrial DNA may partly explain the genetic predisposition to certain medical conditions, probably in a similar way to the mutations of nuclear DNA [5]. Recent researches have proposed that the different mitochondrial haplogroups might play a role in the development of several chronic diseases as well as of cancer [3], [6], [7], [8], [9], [10], [11]. Indeed, since mitochondrial haplogroups are involved not only in mitochondria physiology, but also in cell metabolism, cells or tissues at high consumption of energy (such as also tumor cells) represent one of the main targets of mitochondrial dysfunction [12]. Difference in redox signaling as a consequence of haplogroup-associated oxidative phosphorylation capacity has been also described, highlighting the role of haplogroups in influencing the mitochondrial functions [13]. Notably, modifications in the number, shape and function of mitochondria have been reported in different cancer types. The bioenergetic switch from mitochondrial oxidative phosphorylation to glycolysis has been indicated to be a hallmark of tumorigenesis [12]. Furthermore, retrograde signaling originating from mitochondrial

dysfunction has been suggested to initiate crucial signaling pathways fundamental for cell growth [12].

Aim of our research

Although several studies have already indicated potential associations among particular mitochondrial haplogroups and the risk of cancer development [3], [6], [7], [8], [9], [10], [11], other studies failed to demonstrate such association [14], [15], [16]. However, such studies were almost exclusively cross-sectional or case-control studies, and this may have generated a potential bias. Given this background, we aimed to investigate whether any mitochondrial haplogroups carried a significant higher risk of cancer development in a large prospective cohort of North American people included in the Osteoarthritis Initiative.

Materials and methods

Data source and subjects

All participants in this longitudinal study were recruited as part of the ongoing, publicly and privately funded, multicenter Osteoarthritis Initiative (OAI study) (http://www.oai.ucsf.edu/). Specific datasets used are those recorded during baseline (November 2008) (V00) and those reporting information regarding cancer incidence until the last evaluation available (96 months; V10).

Patients at high risk of knee osteoarthritis (e.g. obese, with familiarity for OA) were recruited from four clinical sites in the US (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. All participants provided written informed consent. The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center, University of California at San Francisco.

The reliability of this cohort for our aim is based on two main considerations. The first is that no association is reported between osteoarthritis and any cancer types. In other words, for our aim such population is comparable to general population. The second is that this cohort reported data on solid cancers (other than skin cancer, leukemia or lymphoma), following the standardized system of the Charleston Comorbidity Scale, but without specifying the tumor type. However, considering that the contemporary conception of cancer is that of a complex genetic disease, a concept of cancer not of the organ but in the organ in which it arises [17], [18], also the dichotomous information cancer yes versus cancer no may be relevant.

Exposure

The haplogroup assignment was performed by a previously published method [19], which consisted in a combination of sequencing and PCR-RFLP techniques. The sequencing technique consisted of the multiplex assignment of the main 6 SNPs that contribute to the generation of the most prevalent Caucasian haplogroups [20] (H, V, super HV, U, K, T, J) following the single base extension (SBE) assay. All the mitochondrial haplogroups have been named following this nomenclature in agreement with those suggested by the OAI (http://www.oai.ucsf.edu/): H, U, K, J, T, V, SuperHV, I, W, X or Others. After that, we group these haplotypes following the classification suggested by MITOMAP [21] in three subgroups of the superhaplogroup N family: H, T, U, V, W, X; I, J, K; superHV/others (Fig. 1).

Outcomes

Our outcome of interest was the incidence of any cancer during follow-up period. A doctor asked the participants if they had any cancer (other than skin cancer, leukemia or lymphoma). This information was recorded during the follow-up visits number V03, V06, V08, and V10.

Covariates

A number of variables were identified from the OAI dataset to explore the relationship between mitochondrial haplogroups and incident cancer. These included: (1) physical activity evaluated through the Physical Activity Scale for the Elderly [22]. This scale, validated in older populations, covers 12 different activities, such as walking, sports, and housework, and is scored from 0 to 400 and more; (2) smoking habits as "previous/current" versus never; (3) educational level was categorized as "degree" versus others; (4) yearly income as <versus≥ 50,000 $ or missing data; (5) co-morbidities assessed through the modified Charlson comorbidity score, with higher scores indicating an increased severity of conditions [23]; (7) body mass index (BMI), as recorded by a trained nurse; (8) depressive symptoms derived from the 20-item Center for Epidemiologic Studies-Depression (CES-D) instrument [24]. The range of possible values for this score is 0 to 60, where higher scores indicate more depressive symptoms [24].

Statistical analyses

Since the interaction gender by mitochondrial haplogroups, taking incident cancer as outcome, was significant ($p < 0.0001$ in the Cox's regression analysis), all the data are reported by sex. For continuous variables, normal distributions were tested using the Kolmogorov–Smirnov test. The data are shown as means and standard deviations (SD) for quantitative measures, and number with percentages for all discrete variables by mitochondrial haplogroups.

For continuous variables, Analysis of Variance (ANOVA) with the Bonferroni's correction was used, whilst logistic regression analysis was applied for discrete variables. In all the analyses, the haplogroups H, T, U, V, W, X were taken as reference, being the most frequent in both sexes. Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, then Welch's ANOVA was used.

The strength of the association of mitochondrial haplogroups and incident cancer was assessed through a Cox's regression analysis. Factors significantly associated with incident cancer or significantly different across mitochondrial haplogroups (taking a p-value < 0.05 as statistically significant) were included. Multi-collinearity among covariates was assessed through variance inflation factor, taking a cut-off of 2 as a reason of exclusion, but no variable was excluded due to this reason. The basic model was not adjusted for any confounders, whilst the fully adjusted model included baseline values of: age, BMI, Physical Activity Scale in the Elderly (PASE) score, CES-D score, Charlson comorbidity index as continuous variables, education, smoking habits, yearly income as categorical variables. Data of Cox's regression analysis were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

All analyses were performed using the SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value < 0.05.

Results

Study participants

At baseline, among 4796 potentially eligible individuals, 1047 subjects did not have a mitochondrial DNA assessment, 126 did not have this assessment for technical problems, 186 had cancer at baseline and 215 were lost at follow-up. Thus, 3222 participants were included in the analysis.

Baseline analyses

The 3222 participants included aged a mean of 61.3 ± 9.3 (range: 45–79) years, with a higher prevalence of women (1816 = 56.4%). All participants were Caucasians.

The baseline characteristics of the participants by gender and mitochondrial haplogroup are shown in Table 1. In men, taking participants with H, T, U, V, W, X haplogroup as reference (n = 1085), participants with superHV/other haplogroups (n = 77) reported significant lower PASE score ($p = 0.001$) and those with I, J, K haplogroup (n = 244) a significant lower prevalence of previous/actual smokers (Table 1, **left side**). In women, no statistical differences emerged across mitochondrial haplogroups.

Association between mitochondrial haplogroups and incident cancer

After a median period of 8 years, 171 men and 169 women developed cancer equal to 10.6% of the baseline population.

As reported in Fig. 2, women having I, J, K haplogroup (n = 345) reported a significant higher incidence of cancer compared to people with H, T, U, V, W, X haplogroup (n = 1371) and superHV/others (n = 100) ($p < 0.0001$), whilst in men non association was found ($p = 0.60$) (other details not shown).

Using a Cox regression analysis, adjusted for eight potential confounders at baseline, with those having the haplogroup H, T, U, V, W, X, women having I, J, K mitochondrial haplogroup reported a 50% increased risk of cancer (HR = 1.50; 95%CI: 1.04–2.16; $p = 0.03$). In men, no significant association between mitochondrial haplogroups and cancer was found (Table 2).

Discussion

Female-specific association among haplogroups and risk of cancer

The main finding of our work is represented by the fact that the 345 women having I, J, K haplogroup reported a significant higher incidence of cancer compared to people with H, T, U, V, W, X haplogroup (n = 1371) and superHV/others (n = 100) (Fig. 2). In the multivariate analysis, women having I, J, K mitochondrial haplogroup reported a 50% increased risk of cancer (HR = 1.50; 95%CI: 1.04–2.16; $p = 0.03$). Notably, this association was not significant in men.

Recent works have pointed out that certain haplotypes are significantly associated with particular tumor types, above all female-specific tumor types (breast and gynecological cancer [11], [25], [26], [27], [28]), while there are no association among haplogroups and male-specific tumor types (prostate and testicular cancer) [14], [15], [16], [29]. Our findings may be interpreted in the light of

these recent works, further highlighting the gender-specific role of haplogroups in influencing the risk of cancer development in females. It has also to be recognized that for some tumor types, there are no specific associations among any haplogroups and patients' gender (e.g. lung cancer and gastric cancer) [30], [31].

For male-specific tumors, Giorgi et al. in a cohort of over 7,000 people found no association between any haplogroups and overall prostate cancer risk [29]. Similar findings were replicated by Mueller et al. [15] and also by Avarez-Cubero et al. [16] At the same time, also Ewis et al. [14] did not find any association between particular haplogroups and risk of testicular germ-cell tumors. Conversely, for female-specific cancers, other papers have recently indicated a significant association among specific haplogroups and risk of tumors. Li et al. have indicated a specific sub-haplogroup, the D4b1 typical of Chinese population, as associated with cervical tumorigenesis [28]. Also another recent paper highlighted the role of haplogroups in cervical cancer, indicating that a de-regulation of mitochondrial genes may be involved in the development of such cancer [27]. Earp et al. furthermore, described a strong association between specific inherited common variants of mitochondrial DNA and serous ovarian cancer risk [25]. Several other authors, lastly, definitively clarified that peculiar haplogroups are associated with a specific risk of breast cancer [11], [16].

Potential associations among female-specific oncogenesis and haplogroups

This gender-specific association may be partly explained by the intimate correlation between mitochondrial haplogroups and mutational status of *BRCA* (Breast Cancer) genes. Indeed, Tommasi et al. indicates that mitochondrial haplogroup X is the most frequent haplogroup in *BRCA1*-mutated carriers, and the haplogroup H as significantly linked to *BRCA2*-mutated carriers [11]. Such genes are known to be involved in the oncogenesis of breast and ovarian cancer, and their mutational status (both somatic and germline) can now be determined very accurately with next-generation sequencing [32]. It may be useful in the future, also on the basis of our work, to integrate the pathology report not only with *BRCA* genes or other genes (so called "next generation diagnosis" [33]) mutational status, but also with a characterization of mitochondrial haplogroups. Indeed, above all for genetic material that has a specific gender-association or a maternal inheritance (e.g. *BRCA*-associated protein gene, that is mostly mutated in females, mitochondrial haplogroups, etc.), there are also important implications for screening, follow-up and therapy [34], not only of patients but also for their relatives. Blein et al. identified mitochondrial haplogroup T1a1 as inversely associated with breast cancer risk in *BRCA2* mutation carriers, further highlighting the relationship among haplogroups and BRCAness [35]. These findings have not been confirmed by Gutierrez-Povedano et al. however, that indicated no correlation between haplogroups and *BRCA* genes mutational status [36]. Although the complex mitochondrial landscape has not been fully explained, our work, in which the risk of cancer is strongly associated with gender and haplogroups, seems to further support a possible association among mitochondrial haplogroups and mutational status of genes strongly associated with female-cancers. However, in our analysis, the haplogroups with the highest risk are I, J and K. This difference may reside in the different populations studied, involving our cohort North-American people and not European people as for Tommasi et al. [11], for example.

Strengths and limitations of our research

The findings of our paper should be interpreted within its limitations. First, the OAI included only people with or at high risk of knee osteoarthritis and so it could be not fully representative of the general population. However, since no association is reported between osteoarthritis and any cancer types, for the specific aim of cancer research this cohort is comparable to general population with a certain degree of reliability. Second, this cohort reported data on solid malignancies, but without

specifying the tumor type during follow-up, and the information are self-reported. However, as already indicated in the Methods section, also the dichotomous information “cancer yes” versus “cancer no” may be relevant to assess the genetic impact of mitochondrial haplogroups on cancer epidemiology. The self-reported method is not an improvised system, but follows strictly the standardized method of the Charleston Comorbidity Scale. Moreover, the agreement between self-reported information and registry-confirmed diagnoses is high, indicating that self-reported information can be used as good proxy for the real presence of cancer [37]. About the tumor-types, the lack of the distinction of the specific tumor-types does represent a limitation of our work. However, in our opinion, this study may have the merit to suggest a certain predisposition of a female subpopulation to cancer in general. This preliminary report calls for future studies that should explore more in depth not only the peculiar association among some haplogroups and cancer in women, but also the possible presence of a specific cancer type in this subpopulation. Third, the number of people in some haplogroups is limited, but to go beyond this limitation we grouped the haplogroups in three distinct supergroups, following the indication of MITOMAP [21]. To further support the reliability of this research, furthermore, we highlight as strengths of our work the length of follow-up (median period: 8 years), the longitudinal design, the substantial number of eight confounders considered in multivariate analysis, and also a significant sample size.

Conclusions

In conclusion, we have reported a strong association among haplogroups I, J and K and risk of cancer in women, highlighting the potential role of mitochondrial genetics in influencing the predisposition to cancer in general, and that the risk of cancer based on particular mitochondrial haplotypes may be relevant in female subject only. The overall message of this paper is indeed about cancer in general, which now should be conceived not more as a specific disease of a specific organ (e.g. cancer of the breast, cancer of the colon, etc.) but as a general and genetic disease in a specific organ (e.g. cancer in the breast, cancer in the colon, etc.) [37], [38] Also in the light of this observation, the predisposition of women with certain haplogroups merits and warrants consideration by the scientific community. Further studies are needed to completely understand the complex network of associations among mitochondrial haplogroups, oncogenes and gender. Future screening program may also taken into account the analysis of such haplogroups to address particular strategies of cancer prevention.

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